characteristics of the cohort based on the presence or absence of depression has been previously published.[5] Given the lack of correlation between these variables and depression in bivariate models, these variables were not included in the multivariable model. In addition, the number of events (52) limited the inclusion of too many covariates at the risk of over-fitting the model. We agree with Brown that perhaps one mediator between depression and poor outcomes could be that those with depression are more non-adherent to dietary and fluid restrictions, which in turn leads to worse outcomes.[6] Future larger studies are warranted to address these important questions.

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Bilirubin as a predictor of albuminuria and atherosclerosis in type 2 diabetic patients: misleading data

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To the Editor: We read with great interest the article by Fukui M and colleagues[1] evaluating the relationship between serum bilirubin and albuminuria in patients with type II diabetes. In this paper, the authors performed a number of correlations and a multiple regression analysis and concluded that the serum bilirubin level is associated with microalbuminuria and subclinical atherosclerosis in type II diabetic patients.

However, these results should be interpreted with caution, as in most of the correlations, the Pearson's r value was below 0.2, implying a very poor correlation.[2] For example, the coefficient of determination (r^2) for bilirubin pulse wave velocity and bilirubin ankle brachial index, which are early preclinical markers of atherosclerosis, are $0.114^2 = 0.013$ and $0.118^2 = 0.0139$, respectively. That is, the proportion of variance that the variables have in common is 1.3 and 1.39%, respectively; the remaining 98.7 and 98.61% would probably be explained by other factors, perhaps by HbA1c levels or other parameters common and sufficiently proven to be atherogenic in diabetic patients. The fact that these weak correlations were statistically significant can be explained by the large sample size of the study but does not mean that these values are fair enough to imply any important correlation between the examined variables. Similarly, the adjusted R^2 as well as the tolerance values in the multiple regression model should be presented, as there seems to be a degree of co-linearity (between age and duration of diabetes, BMI, or systolic blood pressure) that might destabilize the model and lead to indefinite results (for example, triglycerides but not cholesterol were independent determinants of log (urinary albumin excretion)).

In our opinion, it is quite venturesome and unwarranted to discuss the potential preventive and therapeutic applications of bilirubin or its diagnostic utility as a new risk factor for diabetic nephropathy and atherosclerosis based on the current data.

1. Fukui M, Tanaka M, Shiraishi E *et al.* Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. *Kidney Int* 2008; **74**: 1197–1201.
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Response to 'Bilirubin as a predictor of albuminuria and atherosclerosis in type 2 diabetic patients: misleading data'

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We would like to thank Drs Kassimatis and Moutzouris[1] for their interest in our article,[2] and the editor for the opportunity to clarify the several points raised.

Certainly, the Pearson's r-value between serum bilirubin concentration and pulse wave velocity and between serum

bilirubin concentration and ankle–brachial index were low (<0.2). Those correlations were weak but significant probably because of the large sample size of the study, as Dr Kassimatis *et al.* pointed out.

The main outcome of this study was the negative correlation between serum bilirubin concentration and degree of urinary albumin excretion ($r = -0.202$, $P < 0.0001$), which is a useful marker of diabetic nephropathy. The adjusted R-square was also low ($R^2 = 0.222$, $P < 0.0001$). However, to our surprise, the strength of serum bilirubin concentration as an independent determinant of log (urinary albumin excretion) was similar to those of known factors such as systolic blood pressure, HbA1c, and duration of diabetes in multiple regression analysis.

We believe that serum bilirubin concentration could be a protective marker for diabetic nephropathy and atherosclerosis in patients with type 2 diabetes. Large prospective trials are needed to better assess the effects of bilirubin on diabetic nephropathy and atherosclerosis in patients with type 2 diabetes.

1. Kassimatis TI and Moutzouris DAA. Bilirubin as a predictor of albuminuria and atherosclerosis in type II diabetic patients: misleading data. *Kidney Int* 2009; **75**: 862.
2. Fukui M, Tanaka M, Shiraishi E *et al*. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. *Kidney Int* 2008; **74**: 1197–1201.

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Relationship between serum bilirubin and kidney function in non-diabetic and diabetic individuals

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To the Editor: We read with interest the article by Fukui *et al.*[1] showing that serum bilirubin was positively associated with estimated glomerular filtration rate (e-GFR), and negatively associated with albuminuria in 633 Japanese type 2 diabetic adults, thus suggesting a renoprotective effect of bilirubin.

To further investigate the association between serum bilirubin and kidney function, we performed a retrospective analysis on the database of our laboratory to retrieve results of fasting serum bilirubin, glucose, and creatinine tests that were performed on consecutive adult outpatients (aged >35 years) referred by general practitioners for routine blood testing over the last 6 months. Similarly to the Fukui *et al.* study,[1] patients with bilirubin >1.2 mg/100 ml or creatinine >2.0 mg/100 ml were excluded from the study.

Cumulative results for bilirubin and other variables were retrieved for 2678 adult outpatients (mean age: 55 ± 18 years; 43% male patients), 210 of whom had type 2 diabetes. Serum bilirubin concentrations were negatively associated with e-GFR levels, as estimated by the Modification of Diet in Renal Disease equation, in both non-diabetic ($r = -0.17$; $P < 0.0001$) and diabetic patients ($r = -0.14$; $P < 0.05$). Accordingly, compared to participants with normal kidney function, serum bilirubin concentrations were higher ($P < 0.001$) in those with e-GFR ⩽60 ml/min per 1.73 m^2 in both non-diabetic and diabetic groups, independent of age and gender.

Our findings are in contrast to the results by Fukui *et al.*,[1] and indicate that increased serum bilirubin concentrations, even within the reference range, are significantly associated with decreased kidney function in an unselected outpatient cohort of Caucasian non-diabetic and diabetic adults.

1. Fukui M, Tanaka M, Shiraishi E *et al*. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. *Kidney Int* 2008; **74**: 1197–1201.

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Response to 'Relationship between serum bilirubin and kidney function in non-diabetic and diabetic individuals'

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We would like to thank Targher *et al.*[1] for the interest in our article[2] and the editor for the opportunity to clarify the several points raised.

We are surprised to see their data, which are in contrast to our result. We cannot be certain of the reason for this disparity. The possible explanations for this disparity are as follows. First, mean age (64 ± 12 vs 55 ± 18 years) and the proportion of male gender (52 vs 43%), which were determinants of estimated glomerular filtration rate, were greater in our study compared to those in their study. Second, serum bilirubin concentrations were significantly associated with duration of diabetes, diastolic blood pressure, and serum triglyceride concentration in our study. The differences in those factors as well as in